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Early View

Research letter

Improved ventilatory efficiency to evidence haemodynamic improvement after balloon pulmonary angioplasty in chronic thromboembolic pulmonary hypertension

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Improved ventilatory efficiency to evidence haemodynamic improvement after balloon pulmonary angioplasty in chronic thromboembolic pulmonary hypertension.

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Running Title: *Ventilatory efficacy to demonstrate PVR improvement after BPA in CTEPH*

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To the Editor,

Chronic thromboembolic pulmonary hypertension (CTEPH) is a progressive pulmonary vascular disease that results from the association of occlusion of large pulmonary arteries by persistent thrombi and of distal small-vessel vasculopathy, leading to increased pulmonary vascular resistance (PVR) [1]. Heightened PVR contributes to limit cardiac output during exercise, resulting in a decreased capacity for aerobic exercise [2]. In selected CTEPH patients, balloon pulmonary angioplasty (BPA) has recently become a recognized therapeutic option that aims at decreasing PVR, allowing improvements of symptoms, exercise tolerance, exercise capacity and survival [3, 4].

Change in PVR has been the primary endpoint of major trials of either PH-drugs and/or BPA in CTEPH [5–7]. Calculation of PVR requires a right heart catheterization (RHC), a procedure that gives accurate and reproducible measurements and that therefore requires few patients to power clinical trial endpoints. However, the invasive nature of RHC may prevent its use in routine care, and non-invasive exercise tests that reflect the haemodynamic effects of CTEPH treatments may be preferred to assess patients. The change in 6-minute walk distance (6MWD) is the most commonly used parameter for quantifying the effects on exercise capacity of interventions aimed at improving haemodynamics [6, 8]. Nevertheless, although measurement of 6MWD is considered easy to perform in most clinical settings, this parameter suffers from several weaknesses: (i) within-subject variability is high; (ii) since there is a "ceiling effect", it is very unlikely that patients whose 6MWD was preserved before treatment will show a change in 6MWD after treatment, despite improvement in haemodynamic parameters; (iii) apart from haemodynamic changes, variations in 6MWD may depend on certain patient characteristics such as size, sex and age [9, 10]. Cardiopulmonary exercise testing (CPET) has also been proposed to evaluate therapeutic interventions in CTEPH patients [9]. CPET quantitates aerobic capacity (peak oxygen uptake

[$\dot{V}O_2$]) and ventilatory inefficiency (excessive ventilation [$\dot{V}E$] with respect to CO_2 output [$\dot{V}CO_2$]) and might provide a more accurate physiologic assessment than 6MWD [9]. Nevertheless, CPET is still much less used than 6MWD, probably because it is considered more difficult to perform and interpret [9].

In the current study, we sought to identify whether the changes in PVR (pre- *vs.* post-BPA) were best reflected by changes in 6MWD, peak$\dot{V}O_2$ or ventilatory efficiency. To do that, we analysed a group of 38 patients referred for BPA at our institution between September 2020 and December 2021. Eligibility criteria for angioplasty and techniques used to perform BPA were described elsewhere [3]. Since confounding factors such as peripheral adaptation and improved deconditioning resulting from increased physical activity in daily life under improved haemodynamics may contribute to improve 6MWD and peak$\dot{V}O_2$ [11], patients who were evaluated post-BPA more than 3 months after the last BPA session were not included. Patients who had any change in PH-targeted therapy between the two evaluations (pre- and post-BPA), patients with an obstructive ventilatory disorder and/or interstitial lung disease, and/or patients with a left heart disease were also excluded [1]. Ventilatory efficiency was represented in 2 ways, (i) the nadir of the $\dot{V}E/\dot{V}CO_2$ ratio during exercise and (ii) the $\dot{V}E/\dot{V}CO_2$ ratio at peak exercise. Associations between changes in PVR on one hand and changes in 6MWD and CPET parameters on the other hand were assessed through univariate and multivariate linear regression models. Two analyses were performed depending on the criterion used to assess ventilatory efficiency (nadir or peak $\dot{V}E/\dot{V}CO_2$). The study protocol was approved by the Institutional Review Board (Comité de Protection des Personnes Sud-Est V, 2013-AO1036-39) and patients provided written informed consent.

The mean age (± standard deviation) of the 38 patients included was 67±11 years, the mean interval between the 2 evaluations was 3.2±2.3 months (4.5±1.8 BPA sessions per patient; 4.1±1.3 dilated vessels per procedure) and 30/38 patients were receiving at least one PH-

targeted drug. Comparisons between pre- and post-BPA were the following: PVR decreased (573±276 *vs.* 290±111 dyn.s.cm^{-5}; *P*<0.001), 6MWD increased (394±112 *vs.* 429±94 m; *P*<0.001) and peak $\dot{V}O_2$ increased (1.10±0.34 *vs.* 1.31±0.32 L.min^{-1} and 14.4±3.6 vs. 17.1±3.7 mL.kg^{-1}.min^{-1}; *P*<0.001). Of note, partial oxygen pressure at peak increased (60±11 *vs.* 69±13 mmHg; *P*<0.001) but respiratory exchange ratios at peak were similar pre- and post-BPA (1.07±0.13 and 1.07±0.12, respectively; *P*=0.83). Nadir $\dot{V}E/\dot{V}CO_2$ decreased from 49.3±12.7 to 42.8±11.8 (*P*<0.001) and $\dot{V}E/\dot{V}CO_2$ at peak exercise decreased from 57.8±16.7 to 48.0±12.6 (*P*<0.001). Changes in 6MWD did not correlate significantly with changes in PVR (r=0.23, *P*=0.17). Changes in peak $\dot{V}O_2$, nadir $\dot{V}E/\dot{V}CO_2$ and $\dot{V}E/\dot{V}CO_2$ at peak exercise correlated with changes in PVR (r=0.39, *P*=0.02; r=0.61, *P*<0.001 and r=0.81, *P*<0.001, respectively). In multivariate analysis, only the $\dot{V}E/\dot{V}CO_2$ ratio correlated with PVR, with the best model being with peak $\dot{V}E/\dot{V}CO_2$ as a criterion of ventilatory efficiency (Table 1).

There is currently no definition of success after BPA [12]. Nevertheless, as change in PVR is being used as the primary endpoint of many major trials in CTEPH [5–7], we used this endpoint to quantify treatment success in our analysis. We found no significant correlation between the change in PVR and the change in 6MWD, suggesting that the haemodynamic improvement measured at rest did not translate into an improvement in mean walking speed measured during a 6-min walk test. Such an observation has already been made in CTEPH. In a placebo-controlled study, a positive treatment effect of the endothelin receptor antagonist bosentan on resting PVR was demonstrated in inoperable CTEPH patients whereas no significant effect on 6MWD was found [6]. Very recently, another placebo-controlled study involving CTEPH patients demonstrated that the prostacyclin-receptor agonist selexipag significantly improved resting PVR, although 6MWD remained unchanged [5]. Although 6MWD is considered an indirect test of right ventricular function in pulmonary hypertension [2], it is plausible that in patients with CTEPH, whose average age is about 65 years, factors

other than haemodynamics (peripheral factors, including skeletal muscle deconditioning and decreased oxygen extraction) may be involved in the impairment of mean walking speed and its changes after treatment.

The maximal capacity to perform aerobic work can be estimated in patients by the peak $\dot{V}O_2$. According to the Fick principle, peak $\dot{V}O_2$ is equal to the product of the peak value of cardiac output and of arteriovenous oxygen content difference at peak exercise [13]. Assuming that venous oxygen content at peak exercise was unlikely to have varied substantially in our group of patients because muscle remodelling was unlikely to have occurred between the two evaluations, changes in peak $\dot{V}O_2$ after BPA were likely to depend mainly on changes in cardiac output and in arterial oxygen content. Because of this, it is understandable that we found a significant correlation between changes in PVR (which accounts for changes in cardiac output) and changes in peak $\dot{V}O_2$. Nevertheless, because changes in peak $\dot{V}O_2$ and changes in $\dot{V}E/\dot{V}CO_2$ were correlated (r=0.39, *P*=0.01), and the correlation of changes in PVR with changes in $\dot{V}E/\dot{V}CO_2$ was stronger than with changes in peak $\dot{V}O_2$, the latter were no longer significantly associated with resting haemodynamic improvements in the multivariate analysis.

The very strong correlation found here between changes in PVR and changes in $\dot{V}E/\dot{V}CO_2$ in CTEPH patients treated with BPA has previously been reported in CTEPH patients receiving pulmonary endarterectomy [14]. The pathophysiological mechanisms of ventilatory inefficiency in CTEPH are complex and may involve heterogeneity in the matching of regional ventilation and perfusion, autonomic nervous system dysfunction (due, at least in part, to elevated right atrial pressure), altered $PaCO_2$ set-point and dynamic hyperinflation [15]. It is plausible that while improving PVR, BPA also improved these parameters [1], thus explaining our results.

We acknowledge that our results were obtained in highly selected CTEPH patients without cardiorespiratory comorbidity and that a validation in an independent group of patients is required. Another limitation is that haemodynamics were measured only at rest. However, it is plausible that the relationship between $\dot{V}E/\dot{V}CO_2$, peak $\dot{V}O_2$ and 6MWD, and pulmonary resistance measured during exercise may differ from the relationship between these indices and PVR measured at rest. Nevertheless, for the routine practice, our findings suggest (i) that although considered complex to interpret, CPET can allow to obtain simple non-invasive parameters such as $\dot{V}E/\dot{V}CO_2$ that can reflect resting haemodynamic improvements after BPA in CTEPH patients and (ii) that $\dot{V}E/\dot{V}CO_2$ outperforms 6MWD and even peak $\dot{V}O_2$ to evidence these haemodynamic effects.

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Table 1. Simple and multivariate linear regression with the change in pulmonary vascular resistance (PVR) pre- *vs.* post-balloon pulmonary angioplasty (BPA) as the dependent variable and changes in 6-min walking distance (6MWD), in peak oxygen consumption ($\dot{V}O_2$) and in the ratio of expired ventilation on carbon dioxide output ($\dot{V}E/\dot{V}CO_2$) as covariates. In the model 1, $\dot{V}E/\dot{V}CO_2$ measured at peak exercise was used to quantify ventilatory efficiency, while in Model 2, the nadir $\dot{V}E/\dot{V}CO_2$ was used for that purpose.

	Model 1 (with change in peak $\dot{V}E/\dot{V}CO_2$)				**Model 2 (with change in nadir $\dot{V}E/\dot{V}CO_2$)**			
	Univariate analysis		**Multivariate analysis**		**Univariate analysis**		**Multivariate analysis**	
	Estimate [95% CI]	*P*-value	**Estimate [95% CI]**	*P*-value	**Estimate [95% CI]**	*P*-value	**Estimate [95% CI]**	*P*-value
Change in 6MWD	0.9 [-0.4 : 2.2]	0.17	-0.1 [-0.9 : 0.8]	0.91	0.9 [-0.4 : 2.2]	0.17	0.5 [-0.7 : 1.6]	0.40
Change in peak$\dot{V}O_2$	470.0 [90.8 : 850.0]	0.02	-62.1 [-363.0 : 238.8]	0.68	470.0 [90.8 : 850.0]	0.02	208.9 [-154.3 : 572.0]	0.25
Change in $\dot{V}E/\dot{V}CO_2$	14.5 [10.9 : 18.3]	<0.001	15.0 [10.4 : 19.7]	<0.001	18.0 [10.2 : 25.8]	<0.001	15.1 [6.2 : 24.1]	0.002

Estimate: coefficient that compares the strength of the effect of the change of each individual independent variable (*i.e.*, 6MWD, peak$\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$) to the dependent variable (i.e., change in PVR); 95% CI: confidence interval à 95% of the estimate.

6MWD: 6-min walking distance; peak$\dot{V}O_2$: peak oxygen uptake; $\dot{V}E$: expired ventilation; $\dot{V}CO_2$: carbon dioxide output.